CASE REPORT

Reversal of Dabigatran Bleeding and Coagulopathy Using Idarucizumab in a Patient With Acute Kidney Injury

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ABSTRACT

Idarucizumab is approved for patients treated with dabigatran when reversal of the anticoagulant effects is needed. Like dabigatran, idarucizumab is excreted in the urine. The effect of renal dysfunction on drug elimination is uncertain, as patients in the RE-VERSE AD trial had a median creatinine clearance of 58 mL/min. Also, dabigatran accumulation can occur if the international normalized ratio (INR) is greater than two.

A 73-year-old female was admitted for lower extremity edema and increased abdominal girth. On admission, the patient was in acute kidney injury (AKI) with an estimated creatinine clearance of 34.5 mL/min. Her prothrombin time (PT) on admission was 17 seconds, her INR was 1.4, and her hemoglobin was 8.7 gm/dL (12–16 gm/dL). Throughout her admission, she was continued on her home regimen of dabigatran 150 mg twice daily for atrial fibrillation. On day 4, she had rectal bleeding and altered mental status. At this time, her PT was elevated to 25.6 seconds, her INR had increased to 2.3, and her hemoglobin had dropped to 6.8 gm/dL. Two doses of idarucizumab 2.5 gm were administered, and dabigatran was successfully reversed with cessation of bleeding and normalization of the INR to 1.5. An additional dose of idarucizumab was not required. The patient was discharged home two days later.

Idarucizumab successfully reversed the bleeding and coagulopathy associated with dabigatran in a patient with AKI.

Keywords: anticoagulant, international normalized ratio, creatinine clearance, gastrointestinal bleed, anticoagulant reversal, direct thrombin inhibitor, idarucizumab

INTRODUCTION

Dabigatran is a direct thrombin inhibitor indicated for the prevention and treatment of venous thromboembolism and for stroke reduction in patients with non-valvular atrial fibrillation.[1] Routine INR monitoring is not recommended for patients receiving dabigatran, but case reports have described bleeding and INR elevations, particularly in patients with impaired renal function.[2]

Prior to 2015, there was no reversal agent available for patients needing emergent reversal of dabigatran. Hemodialysis was the only suggested way to reverse dabigatran effects; it was time-consuming and not always feasible in urgent situations in which the patient was bleeding.[1] In 2015, the U.S. Food and Drug Administration (FDA) approved idarucizumab (Praxbind®, Boehringer Ingelheim) for patients treated with dabigatran when the reversal of anticoagulant effects is required for emergency surgery or urgent procedures, or life-threatening or uncontrolled bleeding.[3] Idarucizumab is a monoclonal antibody that directly targets dabigatran. Its approval was based solely on results of the Idarucizumab for Dabigatran Reversal (RE-VERSE AD) trial. Although the FDA-approved dosing does not include renal dose adjustments, idarucizumab clearance may be decreased in patients with impaired renal function as it is excreted in the urine.[3] The effect of renal dysfunction on drug elimination is uncertain, as patients in RE-VERSE AD had a median creatinine clearance of 58 mL/min (11–187 mL/min).[4]

CASE PRESENTATION

A 73-year-old female with a medical history of non-alcoholic steatohepatitis (NASH), cirrhosis, and atrial fibrillation on dabigatran 150 mg twice daily with a $CHADS_2$-Vasc score of 2 (age, sex), degenerative joint disease, asthma, lumbar spinal stenosis, hepatic encephalopathy, and an atrial septal defect was admitted to the emergency department (ED) for increasing shortness of breath. She was also experiencing lower extremity edema and increased abdominal girth. In the ED, the patient denied knowledge of any bleeding. She was admitted to the hospital for hepatorenal syndrome, decompensated congestive heart failure, and abdominal compartment syndrome. On admission, the patient was in AKI with a serum creatinine of 1.4 mg/dL (baseline 1.0 mg/dL). Her creatinine clearance was calculated to be 34.5 mL/min. Her PT on admission was 17 seconds, her INR was 1.4, and her hemoglobin was 8.7 gm/dL (12–16 gm/dL) (Table 1). She remained on her home regimen of dabigatran 150 mg twice daily. On day 4, she began to experience multiple episodes of bright red rectal bleeding and altered mental status. At this time, she was hypotensive with a blood pressure of 98/52 mmHg, a serum creatinine of 1.6 mg/dL, and an estimated creatinine clearance of 29.15 mL/min. Her PT was elevated at 25.6 seconds, her INR had increased to 2.3, and her hemoglobin had dropped to 6.8 gm/dL. The decision was made to administer idarucizumab, and she received the recommended dose of 2 x 2.5 gm intravenously. She was then taken to the gastrointestinal (GI) suite where she was intubated and underwent esophagogastroduodenoscopy and flexible sigmoidoscopy. She was presumed to have a lower GI bleed and received two units of packed red blood cells. Fourteen hours following idarucizumab administration, her PT was 18.3 seconds, her INR was 1.5, her serum creatinine was 1.5 mg/dL, and her creatinine clearance was 31.1 mL/min. She remained intubated and underwent colonoscopy. Per the GI note, there was no fresh or old blood throughout the colon or ileum, and the etiology of

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Table 1 Case Patient's Laboratory Test Values

Parameter	Standard Values	Admission (Day 1)	Before Idarucizumab (Day 4)	14 Hours After Idarucizumab (Day 5)	Discharge (Day 9)
PT (sec)	11.8–14.3	17	25.6	18.3	20.5
INR	0.9–1.1	1.4	2.3	1.5	1.8
Serum creatinine (mg/dL)	0.7–1.2	1.4 (baseline 1.0)	1.6	1.5	1.0
Calculated creatinine clearance (mL/min)	-	34.5	29.15	31.1	51.3
Hemoglobin (gm/dL)	12–16	8.7	6.8	8.2	7.7

PT = prothrombin time; INR = international normalized ratio.

blood loss was unclear. Ultimately, the decision was made not to reinitiate anticoagulation. She was extubated on day 6 and discharged home on day 9.

DISCUSSION

Although Sauter et al. described the use of idarucizumab for dabigatran reversal prior to urgent surgery, in a patient with a glomerular filtration rate (GFR) of 36.5 mL/min, this case shows the successful reversal of dabigatran bleeding and coagulopathy in a patient with AKI and a presumed GI bleed.[7]

The decision was made to administer idarucizumab to this patient because prior to administration, she was hypotensive, had a drop in hemoglobin of 1.9 gm/dL, and her PT and INR were elevated. Also, as the elimination half-life of dabigatran is prolonged in patients with impaired renal function, her acute decline in renal function had likely contributed to the bleeding episode. While hospitalized, the patient had her lowest creatinine clearance (29.15 mL/min) on the day of idarucizumab administration, which is much lower than the creatinine clearance of 57 mL/min seen in the case by Mourafetis et al., in which a patient had also received idarucizumab for a GI bleed.[8] Prior to her bleed, she was maintained on her home dose of dabigatran 150 mg twice daily, which is the current recommended dose for patients with a creatinine clearance greater than 30 mL/min. On day 4, her calculated creatinine clearance was 29.15 mL/min. The dabigatran dose was not changed to the FDA-approved dose to accommodate this decrease. There are no recommendations in idarucizumab's labeling for renally impaired patients.[3]

Clinical data are limited regarding the use of idarucizumab in patients with AKI. In the RE-VERSE AD trial, 13% of patients had a creatinine clearance of less than 30 mL/min.[4] Notably, although idarucizumab is a monoclonal antibody, once it binds to dabigatran, it must also be renally eliminated.[3] This raises a concern for patients who receive idarucizumab and dialysis with the potential rebound in coagulation parameters post-excretion of idarucizumab. In Marino et al.'s case, the patient received 5 gm of idarucizumab and dialysis, had a rebound in her coagulation parameters, and required a second dose of idarucizumab.[6] Per the prescribing information, idarucizumab should be cleared within 24 hours of administration, and coagulation parameters should return to normal.[3] In our case, the patient received the FDA-approved dose of idarucizumab and her coagulation parameters returned to normal within the expected 24 hours, despite her renal dysfunction. The bleeding resolved and she was hemodynamically stable, requiring no further doses of idarucizumab.

Importantly, this patient also had an elevated INR of 2.3 on the day of the presumed GI bleed. Dabigatran's effect is concentration-dependent; concentrations will depend on dose, absorption, and clearance through the kidney and will differ among patients. Some studies suggest that dabigatran accumulation can increase the INR to greater than 2.[5] In our patient, the elevated INR could have been a result of her impaired renal function and of dabigatran accumulation, rather than her cirrhosis, as her INR was normal at baseline. In a case reported by Kim et al., a 58-year-old Caucasian male receiving dabigatran 150 mg twice daily, with a history of atrial fibrillation and end-stage renal disease on dialysis, presented to the ED with epistaxis and an INR of 8.8. Dabigatran was stopped, he did not receive idarucizumab, and his INR returned to normal five days after admission, demonstrating that dabigatran accumulation can elevate the INR in patients with impaired renal function.[2] In our case, dabigatran was stopped and idarucizumab was given, contrary to Kim et al.'s patient. Our patient's INR returned to normal within 14 hours of idarucizumab administration compared to the five days in Kim et al.

CONCLUSION

Idarucizumab successfully reversed the effects of dabigatran in a patient with AKI. The patient received the FDA-approved dose of idarucizumab and her coagulation parameters returned to normal within 24 hours, as expected.

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